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Antithrombotic Therapy with Low Molecular Weight Heparin in Cancer Patients

G. Petralia and A. K. Kakkar

Department of Surgical Oncology and Technology, Imperial College, Hammersmith Hospital, London, UK

Abstract: Thrombosis is a common complication in patients with cancer. Low molecular weight heparins have been shown to be effective in both the prevention and treatment of venous thromboembolism in the cancer patient. More recently, studies have confirmed the benefits of extended duration of LMWH in the primary prevention of VTE after cancer surgery and for up to six months therapy for acute symptomatic VTE treatment. Beyond these well established uses for LMWH in the prevention and treatment of thrombosis in cancer patients, contemporary studies have demonstrated that LMWH therapy can prolong survival in patients with solid tumour malignant disease.

Key words: cancer; venous thromboembolism; prevention; therapy

Introduction

The intrinsic characteristics of cancer population complicates the oncologist's efforts even further, we must remember that those patients are often debilitated and frequently immobile whilst undergoing procedures which render them bed bound, be those surgical or chemo/radio-therapeutic. In this picture a pivotal role is played by venous thromboembolism (VTE), whose association with malignant disease was first described by Armand Trousseau in 1865 [1] in his original description of the syndrome of thrombophlebitis migrans. This, as a clinical entity, has now been recognised as pathognomonic of underlying cancer, and there is also a growing appreciation that thromboembolic events may be the first clinical manifestation of undiagnosed malignancy [2-4]; as a matter of fact two large studies found the incidence of cancer in patients with idiopathic VTE to be 1.3 times and 3.2 times higher amongst the Danish and Swedish population respectively [5, 6].

Pathogenesis of Venous Thromboembolism in Cancer

It was Virchow, a contemporary of Trousseau, who studied thrombus formation leaving us the legacy of its famous triad: venous stasis, vascular trauma and blood hypercoagulability [7]. The same principles apply to the oncological population with some specific additional issues.

Starting with the latter, the well-known hypercoagulable state found in malignancy has multifactorial origin. Tumour cells have been shown to express procoagulant molecules, the most common being:

- Tissue factor (TF), the physiological transmembrane receptor protein at the base of the extrinsic coagulation pathway that in turn can lead to subclinical or overt thrombosis in some cases or disseminated intravascular coagulation (DIC) in others [8-10].
- Cancer procoagulant (CP), a cysteine protease capable of direct activation of factor X [11] and activating platelets in a thrombin-like fashion [12].

Malignant cells can also promote coagulation indirectly by releasing inflammatory mediators, the most important being tumour necrosis factor (TNF) and interleukin-like proteins (such as IL-1) [2]. These are active on endothelial and mononuclear cells stimulating the secretion of procoagulant molecules that may also have a role in platelet activation [12].

It is common sense to expect venous stasis by external compression in presence of a cancerous mass, or stasis and vascular trauma from direct invasion of a blood vessel, like thrombosis of the Inferior Vena Cava in renal cell carcinoma [13].

Some tumours can induce angiogenesis producing a network of aberrant vessels that create a maze where flow is slowed and disordered, clearance of activated coagulation factors is impaired and hypoxia is present [2].

Radiotherapy further contributes to the thromboembolic risk; in a study on patients with rectal cancer receiving neo-adjuvant radiotherapy, for example, an increased VTE rate was reported during the first 30 days following the planned surgery [14]. Comparable results were found when a five-year follow up study was carried out on similar patients (7.5% vs. 3.6%; $p = 0.001$) [15].

Much better documented is the prothrombotic effect of certain chemotherapeutic agents that may in part be mediated by damage to the endothelial cells [16]. For instance trials relating to the treatment of breast cancer reported an incidence of VTE ranging from 1.7% to 17.6%. VTE risk has

been shown to increase when combination chemotherapy is administered as reported in Levine's review of stage II breast cancer patients [17]. Like radiotherapy, perioperative chemotherapy increases VTE risk: postmenopausal women with stages I and II breast cancer undergoing surgery were divided in two groups accordingly to whether they were to receive post-operative chemotherapy or not, the latter showing statistically significant decreased VTE rates (0.7% vs 2.3%, p = 0.001) [18, 19]. Tamoxifen was also proven to increase DVT risk both in premenopausal (2.3% vs 0.8%, p = 0.003) and postmenopausal (8.0% vs 2.3%, p = 0.003) women [19]. Furthermore tamoxifen in association with chemotherapy increased DVT risk when compared to tamoxifen alone in a group of stage II breast cancer from 1.4% to 9.6% (p = 0.0001) [20].

The increasing use of central lines in cancer patients to deliver chemotherapy, parenteral nutrition, blood and its derivatives or simply as access, further contributes to the thromboembolic risk [21, 22].

Epidemiology of Venous Thromboembolism in Cancer

The clinical spectrum of VTE ranges widely from asymptomatic deep vein thrombosis (DVT) to fatal pulmonary embolism (PE), and the cancer population is burdened with an increased risk of thrombosis recurrence and haemorrhage.

Evidence suggests that 15% of cancer patients will suffer a symptomatic thromboembolic event [11, 23, 24]; and 6% of inpatient bed-days in medical oncology wards are used by those patients due to their VTE [23]. Not only is it the second commonest cause of death in patients with cancer [11, 24], but also one in seven of those patients will die of avoidable fatal PE [25] with up to 60% of thromboembolic deaths occurring at an otherwise favourable time in the history of the cancer. Furthermore it has been estimated that between 9-15% [23] of cancer patients will suffer from DIC requiring intervention.

Tumour histology seems to play a role in determining PE risk: a post-mortem study [26] showed that malignancies of the oesophagus and larynx, myelomatosis and lymphoma to have the lowest rates (0-5% - 6%), followed by stomach (15.2%), extrahepatic biliary system (31.7%), and finally ovarian cancer (34.6%) in pole-position.

Surgery is a well-known risk factor for VTE and that is even more evident in the cancer subpopulation as shown by numerous studies comparing DVT and PE, (fatal PE after major surgery 1.6% vs. 0.4%; $P < 0.05$) [27] in cancer and non-cancer patients. The American College of Chest Physicians [28] collected the evidence on surgical cancer patients over the last 4 decades and found high rates of proximal vein thrombosis and clinical PE, with alarming rates of fatal PE (1-5%), in the absence of any form of thromboprophylaxis, rendering this mandatory in that setting.

To complicate further the therapeutic challenge oncological patients not only present with an increased risk of VTE, but they are also more likely to bleed: 16.1% vs. 7.4% in cancer and non-cancer patients respectively [29]; and to suffer a recurrence with an increased risk 1.72 fold [30]. This was confirmed in a study comparing the outcome of secondary prophylaxis with oral anticoagulants, the incidence of bleeding and recurrence were significantly lower in the non-cancer group compared to the cancer patients: total bleeding 21.6% versus 4.5% (RR 4.5; 95% CI 2.6 - 7.8; $P < 0.0001$); and VTE recurrence was 6.8% versus 2.7% (RR 2.5; 95% CI 0.96-6.5; P = 0.059) [31].

Finally the association of cancer and VTE seems to be associated with poorer outcomes; be that because it is commoner in more aggressive tumours, it is less manageable in the cancer patients or is simply related to the activation of the coagulation cascade and its influence of the tumour biology is still to be determined [32]. Nonetheless six-month death probability goes from 15% in patients with cancer to 80% in patients with both the diagnosis of cancer and VTE [33].

VTE Prevention

An effective prevention programme needs to target underlying factors predisposing to VTE, minimise any secondary effects, be well tolerated by the patient, and feasible both from a logistical and economical point of view [34]. At the moment methods of prophylaxis for VTE in cancer patients show marked regional variations, are infrequently employed in medical oncological patients and in surgical cancer patients maybe omitted due to a fear of bleeding complications [35].

Low dose UFH (LDH) is a commonly used method for prophylaxis against VTE patients in the surgical practice, usually starting about 2 hours preoperatively in a dose of 5000 IU and 8-12 hourly thereafter. Its effectiveness had been proven in cancer patients: in landmark International Multicentre trial, LDH reduced mortality due to PE from 1.6% in the control group to 0.43% in the placebo group [36]. A meta-analysis of studies confirmed this significant reduction in thrombosis rates when compared to placebo from the 30.6% to 13.6%: ; $P < 0.001$) [37].

LMWH, usually administered once daily, has been shown to be at least as effective and safe as LDH administered 3 times daily in studies containing a high percentage of cancer patients. Bergqvist et al. [38] randomised 2097 surgical patients, 66.4% of which with malignant disease, to receive prophylactic treatment for VTE with Dalterparin sodium 2500 U versus 5000 U. Thromboembolic rates decreased in the group receiving the higher dose (8.5% vs. 14.9%; P = 0.001) demonstrating for the first time that efficacy can be improved by an higher dose in cancer patients, who did not present an increased rate of bleeding.

In a study [39] of over three hundred patients undergoing neurosurgery and receiving thrombo-

prophylaxis by means of graduated compression stockings, LMWH was randomised against placebo. About 85% of these patients suffered from tumours of the central nervous system. The results indicated that LMWH was both effective and safe reducing the thromboembolic risk by 50 per cent ($p = 0.004$) without increasing the risk of bleeding complications., when compared to TED stockings alone.

Higher doses of the LMWH Dalterparin 5000 U vs 2500 U were more effective in thromboprophylaxis (8.5% vs. 14.9%; $P = 0.001$) without increasing the bleeding risk [38]. Recently, it has been suggested that prophylaxis should continue for up to for 4 weeks after abdominal or pelvic surgical procedures for cancer. Such extended thromboprophylaxis was associated with a decrease in venographically screened thrombosis rates at 4 weeks from 12.8% in patients receiving in-hospital prophylaxis alone to 4.8% for those receiving extended therapy ($P = 0.02$) [40].

Prevention of VTE in Non-surgical Patients

There are no data that have specifically assessed the value of LMWH for the prophylaxis of VTE in ambulatory cancer patients receiving chemotherapy or radiotherapy. Although the LMWH Dalteparin has been assessed for the prophylaxis of central catheter thrombosis [21] where it was shown to be effective, further studies are required to determine the way in which LMWH could be used most effectively in this large group of cancer patients who appear to be at variable risk of thrombosis over many months of anticancer therapy.

Treatment of Established Venous Thromboembolism

Since thrombosis is such an important complication in cancer patients, treatment of venous thromboembolism remains a major challenge in clinical practice. For instance, incidence of recurrent VTE in cancer patients receiving oral anticoagulant therapy after an acute episode of thrombosis was 20.7% vs 6.8% in patients without cancer (hazard ratio 3.2) [41]. Interestingly, despite this higher incidence for recurrent thrombosis, bleeding complications are also higher in cancer patients receiving oral anticoagulant therapy (12.4% vs 4.9%) in those without cancer [41].

Whether it be cancer or non-cancer patients, the initial treatment of deep vein thrombosis is identical. This is initiated with either intra venous unfractionated heparin dosed to maintain an activated partial thromboplastin time ratio of 1.5 to 2 times laboratory control or subcutaneous low molecular weight heparin provided on a body weight adjusted dosing regimen without need for laboratory monitoring [42]. Recent meta-analyses have demonstrated that low molecular weight heparin is as effective as unfractionated heparin in the initial treatment as assessed by the prevention of recurrent venous thromboembolism (odds ratio 0.85) and is associated with a significant reduction in the risk of bleeding complications (odds ratio 0.57; $P = .05$) [43] Since low molecular weight heparin therapy can be administered subcutaneously without the need for laboratory monitoring it appears to be the agent of choice in the initial treatment of deep vein thrombosis. Indeed, this advantage has allowed for the out patient management of venous thromboembolism in large numbers of patients presenting with this disease including those with cancer.

There are no specific studies which have evaluated efficacy of treatment regimens for the initial treatment of venous thromboembolism specifically in cancer patients. However, large clinical trials have included between 10 and 20% of patients with thrombosis secondary to cancer.

The long term anticoagulation to prevent recurrent venous thromboembolism is usually provided with Vitamin K antagonists. In the cancer patient Vitamin K antagonists have a number of limitations. These include difficulty in maintaining a therapeutic INR [44], need to interrupt oral anticoagulant therapy for thrombocytopenia secondary to disease of therapy, or the need for interventional procedures for management of the cancer. In addition, cancer patients frequently have poor venous access and laboratory regular blood testing from laboratory monitoring in anticoagulation therapy can be difficult and impact on quality of life. Low molecular weight heparins have potential advantages in that they can be provided in a fixed daily dose, in general do not require laboratory monitoring, and their anticoagulant effect can be easily interrupted by omitting a single dose of therapy.

A large international multicentre trial (CLOT in Cancer study) has recently reported the results of a comparison of long term Vitamin K antagonists compared to long term therapy with the low molecular weight heparin Dalteparin Sodium in the prevention of recurrent venous thromboembolism in 676 patients with acute venous thromboembolic disease secondary to cancer [45]. In this innovative study, all patients received Dalteparin Sodium in a dose of 200 IU / kg for an initial 5-7 days of therapy. Those randomised to the Vitamin K antagonist arm were commenced at the same time on Warfarin or Coumadin to maintain a target INR of 2.5. Those randomised to the long term Dalteparin Sodium group continued for the first month on the full treatment dose of this agent. For the remaining 5 months they received therapy in a dose of 75-80% of the initial full treatment dose. The study demonstrated a 52% reduction in the rate of recurrent venous thromboembolic disease in favour of that group of cancer patients who received long term Dalteparin Sodium therapy. There were no significant differences in bleeding complications.

This study has important clinical implications since the impressive reduction in rates of clinical

recurrent venous thromboembolic disease in cancer patients were achieved without any significant increase in bleeding complications. Additionally, the low molecular weight heparin therapy was easier to provide since there was no need for routine laboratory monitoring of anticoagulant therapy.

Low molecular Weight Heparin Therapy and Survival

Speculation over the past 30 years has suggested that anticoagulant therapy and more recently heparin therapy might prolong survival in patients with malignant disease. In a prospective randomised trial 278 patients with small cell lung carcinoma receiving standard anticancer therapy were randomised to receive subcutaneous heparin in full treatment doses in addition to chemotherapy or chemotherapy alone over a 5 week period. There was an improvement in response to chemotherapy from 23% in the no heparin group to 37% in that group of patients who received heparin (P = 0.004) and median survival was increased from 261 days to 317 days (P = 0.001) [46].

More recently retrospective analyses of DVT treatment studies have demonstrated a potential survival advantage for those patients with an acute thrombosis having received low molecular weight heparin for the initial treatment of their thrombosis [43, 47-49].

The first randomised prospective double blind study to evaluate whether the low molecular weight heparin therapy can, indeed, prolong survival in cancer patients with advanced malignant disease (Fragmin Advanced Outcome Study – FAMOUS) has recently reported. In this pioneering study, 385 patients with advanced solid tumour malignancy (the majority having metastatic disease and tumours of primary histological origin in pancreas, colorectal, breast, or ovary) were randomised to receive 5000 units of the low molecular weight heparin Dalteparin Sodium once dialy or a placebo injection for up to 1 year.

The overall survival rate was 41% on the placebo group at 1 year compared to 46% in that group of patients who received Dalteparin Sodium. The study failed to detect the pre-specified 15% difference in mortality at 1 year [50]. In a post hoc sub group analysis of 102 patients who survived beyond 17 months, there was an increase in median survival from 23 months in the placebo group to 43 months in the Dalteparin group. These data must be interpreted with caution since the primary endpoint in the study did not specify a sub group analysis.

More recently the CLOT in Cancer trial [45] has reported an ad hoc analysis of 1 year's survival in patients with acute deep vein thrombosis randomised to receive oral anticoagulant therapy or the low molecular weight heparin Dalteparin for up to 6 months. In this analysis [51] cancer patients without metastasis (N = 150) had a survival advantage if randomised to receive Dalteparin for DVT treatment. This manifested itself as an overall 17% reduction in mortality at 1 year compared to those patients who received 6 months of oral anticoagulant therapy.

These 2 exciting studies are further supported by two contemporary trials which have randomised patients with cancer to receive low molecular weight heparin or no anticoagulant intervention. In the first, in 84 patients with small cell lung cancer, patients received standard chemotherapy with or without low molecular weight heparin Dalteparin in a dose of 5000 units once daily for 18 weeks. The trial demonstrated an overall improvement in survival which was particularly marked for patients with a better prognosis – those with limited disease at the time of presentation. All patients in this trial had small cell lung cancer [52]. In the MALT study, also presented in 2003, 302 patients with a variety of solid cancers were randomised to receive low molecular weight heparin therapy for up to 6 weeks vs a placebo randomisation. Again, this trial demonstrated an overall improvement in survival which was particularly marked for patients with a good prognosis – those defined as having a survival prospect in excess of 6 months at the time of randomisation [53].

Conclusions

Exciting data from prospective randomised clinical trials in cancer patients have now established that low molecular weight heparins are the agents of choice both in the primary prevention of venous thromboembolic disease in cancer patients undergoing surgical intervention and in the treatment and long term secondary prevention of recurrent venous thromboembolism in cancer patients who develop a thrombosis. These agents can be given safely without need, in general, for routine laboratory monitoring in cancer patients. Of particular interest, maybe the additional advantage of low molecular weight heparin therapy – that of prolongation of survival in patients with cancers. These exciting observations on the potential anticancer benefits of low molecular weight heparins have yet to be confirmed in a further series of prospective clinical trials.

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Address for correspondence:
Dr. Ajay K. Kakkar
Department of Surgical Oncology and Technology
Imperial College
Hammersmith Hospital
Du Cane Road
W12 0NN, London
UK
E-mail akkakkar@tri-london.ac.uk